6TH ANNUAL
CHAIR SUMMIT
Master Class for Neuroscience Professional Development

September 26 – 28, 2013 | Westin Tampa Harbour Island

Co-sponsored by
Best Practices in the Management of Bipolar Disorder

Robert M. A. Hirschfeld, MD
University of Texas
Medical Branch
Galveston, TX

Peter C. Whybrow, MD
Director, Semel Institute for Neuroscience and Human Behavior at UCLA
Robert M. A. Hirschfeld, MD

Disclosures

- **Royalties:** Jones and Bartlett Publishers
- **Consultant:** BioStrategies Group: Grey Healthcare Group, Inc.; Merck Manual Editorial Board
- **Honorarium:** BioStrategies Group: CMEology; Health and Wellness Partners; Physicians Post Graduate Press, Inc.
Dr. Whybrow has no disclosures to report.
Learning Objective 1

Initiate therapy in patients with bipolar depression using an evaluation of evidence-based data and best-practice guidelines and recommendations.
Learning Objective 2

Evaluate newly available data regarding the safety and efficacy of therapeutics being investigated for the treatment of bipolar depression.
**Lifetime Prevalence in U.S. General Population**

1-4

- Bipolar I = 1%
- Bipolar II = 1.1%
- Subthreshold bipolar = 2.4%


---

**Major Depression**

- 19%
- 81%

**Bipolar Disorder**

- 4%*
- 96%

* Bipolar I = 1%; Bipolar II = 1.1%; Subthreshold bipolar = 2.4%
Clues to Bipolarity in Depressed Patients

- Family history of bipolar disorder
- 2 or more previous mood episodes
- Younger onset (25 – 30 years) of psychiatric symptoms
- Mania/hypomania during antidepressant treatment
- Current mixed symptoms
- Psychotic symptoms
- Poor response to previous antidepressant treatment

Improved Assessment for Bipolar Disorder Among Depressed Patients

● Ask about history of mania and hypomania
  → “Have you had mood swings?”
  → “Have you ever had a ‘high’ period, where you needed less sleep and had lots of energy?”

● Ask about family history of bipolar disorder

● Involve family members or significant others in the evaluation process

● Screening
  → Consider using a screening instrument for bipolar disorder
  → Example: The Mood Disorder Questionnaire

Diagnostic Accuracy of Bipolar Disorder

- Positive screen rate for bipolar illness: 3.7% (> 6 million people in U.S.)

> 85,000 U.S. Adults Surveyed

96.3% Received Bipolar Dx
3.7% No Bipolar Dx
80% No Bipolar Dx received

Only 20% of those with a positive screen had been told by their doctors that they had bipolar disorder.

Dx = diagnosis.
Bipolar Disorder (BP) Diagnosis Often Missed in Primary Care Settings

- 649 outpatients receiving treatment for depression in the UTMB Family Medicine Clinic

- 67% Never diagnosed BP
- 33% Were previously diagnosed BP
- 21% Screened Positive* for Bipolar Disorder

* Using the Mood Disorder Questionnaire.

UTMB = Telepsychiatry network at the University of Texas Medical Branch.
**FDA-Approved Pharmacological Treatments for Bipolar Depression**

<table>
<thead>
<tr>
<th>Bipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine/Fluoxetine Combo</td>
</tr>
<tr>
<td>Quetiapine</td>
</tr>
<tr>
<td>Lurasidone</td>
</tr>
</tbody>
</table>

Prescribing information for all agents shown available at Drugs@FDA Website. Prescribing information for all agents shown available at Drugs@FDA Website. [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm).
Olanzapine/Fluoxetine Combo For Bipolar Depression in Adults

- **Monotherapy**
  - **Trials:** Two, 8-week, double-blind, placebo-controlled studies of 3 doses
  - **Results:** Positive against placebo and olanzapine monotherapy
  - **AEs:** attention, dry mouth, fatigue, hypersomnia, increased appetite, peripheral edema, sedation, somnolence, tremor, vision blurred, and weight increase

Quetiapine
For Bipolar Depression in Adults

● **Monotherapy**
  → **Trials**: Two, 8-week, double-blind, placebo-controlled studies at two doses
  → **Results**: Positive on both studies
  → **AEs**: somnolence, dry mouth, dizziness, constipation, and lethargy.

● **Adjunctive**
  → **Trials**: Two, double-blind, placebo-controlled studies at two doses as add-on to lithium or divalproex
  → **Results**: Positive on both studies
  → **AEs**: somnolence, dry mouth, asthenia, and constipation

Lurasidone
For Bipolar Depression in Adults

● **Monotherapy**
  → **Trial:** 6 week double-blind, placebo-controlled study of 2 doses (low and high) of lurasidone
  → **Results:** Positive for both doses, starting at week 2
  → **AEs:** Akathisia (8-11%), nausea, sedation

● **Adjunctive**
  → **Trial:** on lithium or divalproex for ≥ 28 days, double-blind, placebo-controlled 6 week study
  → **Results:** Positive, starting at week 3
  → **AEs:** Akathisia (8%), nausea, tremor, somnolence

Common Side Effects for FDA-Approved Treatments for Bipolar Depression

- **Quetiapine**
  - Dry mouth
  - Sedation
  - Somnolence
  - Dizziness

- **Lurasidone**
  - Akathisia
  - Nausea
  - Sedation
  - Tremor
  - Somnolence

- **Olanzapine/Fluoxetine Combo**
  - Weight gain
  - Increased appetite
  - Dry Mouth
  - Asthenia
  - Diarrhea

Prescribing information for all agents shown available at Drugs@FDA Website. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
Non–FDA-Approved Pharmacological Treatments That Have Controlled Evidence Supporting Efficacy in Bipolar Depression

- Lithium
- Divalproex
- Olanzapine
- Lamotrigine

**Adjunctive therapies**
- Bupropion
- Paroxetine
- Other SSRIs
- Venlafaxine
- Modafinil
- Pramiprexole
- MAOIs

SSRI = selective serotonin reuptake inhibitor; MAOI = monoamine oxidase inhibitor.
CANMAT Treatment Guidelines for Acute Bipolar Depression

Monotherapy

- **First-line**
  - Lithium*
  - Lamotrigine*
  - Quetiapine
  - Quetiapine XR

- **Second-line**
  - Divalproex*
  - Lurasidone

- **Third-line**
  - Carbamazepine*
  - Olanzapine**
  - Electroconvulsive therapy

* Not FDA approved for bipolar depression
** Olanzapine in combination with fluoxetine is an FDA approved treatment for bipolar depression

CANMATE Treatment Guidelines for Acute Bipolar Depression

Combination

- First-line
  - Lithium + divalproex*
  - Lithium or divalproex + SSRI*
  - Lithium or divalproex + bupropion*
  - Olanzapine + SSRI**

- Second-line
  - Quetiapine + SSRI*, ¥
  - Adjunctive modafinil*
  - Lithium or divalproex + lamotrigine
  - Lithium or divalproex + lurasidone* ¥

* Combination of agents is not FDA-approved for bipolar depression
** Olanzepine + the SSRI fluoxetine is an FDA approved for bipolar depression
¥ Quetiapine and lurasidone are FDA approved treatments for bipolar depression as monotherapy only

Psychosocial Interventions in the Treatment of Bipolar Disorder

- Psychoeducation
- Regularize biorhythms
- Crisis management
- Family intervention
- Support and advocacy groups
- Supportive psychotherapy
- Behavior management

Resources for Clinicians

- Guidelines and Measures

- Assessment Tools
  - The Bipolarity Index: [http://www.psycheducation.org/depression/STEPBipolarityIndex.htm](http://www.psycheducation.org/depression/STEPBipolarityIndex.htm)
  - Multi-International Neuropsychiatric Interview (MINI): [https://medical-outcomes.com/index/mini](https://medical-outcomes.com/index/mini)

STABLE = The STAndards for BipoLar Excellence Project.
Resources for Patients

- Depression and Bipolar Support Alliance
  → http://www.dbsalliance.org

- National Alliance on Mental Illness
  → http://www.nami.org

- National Institute of Mental Health
Use validated rating scales and questionnaires, in concert with measurement-based care principles, to objectively measure symptoms and response in bipolar depression.
ChronoRecord
Automated Patient Mood-Charting

Patient Care & Research Applications

- Track pattern of disorder
  - Cycle length
  - Frequency
  - Episode type
  - Switching speed
- Track episode triggers
- Track treatment-response
  - New medications
  - Polypharmacy
  - Other treatments
- Reduce missing data
- Reduce administrative costs
- Eliminate data entry errors
- Standardize data
- Reduce patient drop-out rates
- Provide feedback to patients and clinicians
- Accelerate analysis
50-Year-Old Woman With Rapid-Cycling Phenotype

- MOOD
- LIFE EVENTS
- SLEEP
- DRUG REGIMEN
ChronoRecord Software Interface

WELCOME

MOOD

SLEEP

DRUG REGIMEN
49-Year-Old Man With Bipolar II and Alcohol and Cocaine Abuse

Mood

Sleep

Drug Regimen

Drug Legend
#1 Lithium carbonate 300 mg
#2 Carbamazepine 200 mg
#3 Trazodone 100 mg
#4 Clonazepam 1.0 mg
#5 Risperidone 1 mg
22-Year-Old Woman With Bipolar II and Lithium Nonresponse, Lamotrigine Response

**Drug Legend**
- #1 Lithium carbonate 300 mg
- #2 Lamotrigine 25 mg
- #3 Bupropion 100 mg
- #4 Sertraline 100 mg
- #5 Risperidone 1 mg
43-Year-Old Woman With Bipolar I With Response to Lithium & High-Dose Thyroxin

**Drug Legend**

#1 Lithium carbonate 300 mg
#2 Divalproex 500 mg
#3 Paroxetine 40 mg
#4 Levothyroxine - T4 100 mcg
#5 Levothyroxine - T4 200 mcg
64-Year-Old Woman With Bipolar II and Rapid Cycling: What Is the Role of Antidepressant Use?

Drug Legend
#1 Lithium carbonate 300 mg
#2 Venlafaxine 150 mg
#3 Venlafaxine 75 mg
#4 Mirtazapine 30 mg
#5 Diazepam 10 mg
#6 Levothyroxine - T4 25 mg
#7 Conjugated estrogens 1.25 mg
Antidepressants’ Influence on Mood Patterns in Bipolar Disorder: A Naturalistic Study

● Methods
  → Prospective longitudinal study of patients with bipolar disorder over a four-month period using the ChronoRecord
  → 22,662 days of data
  → All (N = 182) were receiving routine outpatient care
    → 104 patients were taking antidepressants
      (95% of those were SSRIs)
    → 78 patients were not taking antidepressants

● Results
  → Comparison across the two groups showed no difference in the daily rate of switching between mood states and no increase in the rapid-cycling phenotype

● Conclusion
  → Antidepressants have little impact on the mood patterns of bipolar patients when taking mood stabilizers

SSRI = selective serotonin reuptake inhibitor
38-Year-Old Woman With Bipolar II and Mood and Sleep Changes With Menstrual Cycle

**MOOD**

**SLEEP**

**DRUG REGIMEN**

- #1 Divalproex sodium 500 mg
- #2 Reboxetine 4 mg
- #3 Sertraline 100 mg
- #4 Sertraline 50 mg
- #5 Lorazepam 1 mg
- #6 Zopicion 7.5 mg
- #7 L-Thyroxin 100 µg
- #8 L-Thyroxin 200 µg

**RESEARCH QUESTIONS**
**Menstrual Cycle-Related Mood Changes in Women With Bipolar Disorder**

- **Design**
  - Group of 17 women consecutively enrolled who entered mood, menstrual data, psychiatric medications, and life events into the ChronoRecord database over a three-month period
  - All women were receiving medication for bipolar disorder
  - 35% were also taking oral contraceptives

- **Results**
  - The majority (65%) of women reported significant mood changes across the menstrual cycle
  - A long menstrual cycle was present in 59% of patients, including those taking oral contraceptives

- **Conclusion**
  - Women taking medication for bipolar disease report lengthening of the menstrual cycle and significant changes in relation to the cycle phase

The ChronoRecord Association
www.chronorecord.com

- Database has over 100,000 days of data for bipolar patients
- Patient software is translated into German, Spanish, Polish and adapted for use in the U.K. and Australia
- Successfully used internationally in Germany, Austria, Chile, Poland, Australia, Canada, U.K.

Publications


Clinical Connections

- Look for clues for bipolarity in depressed patients
- Recent treatment guidelines outline agents that should be used as initial and continuation therapy for bipolar depression
- Couple medication with psychosocial strategies to improve outcomes for patients with bipolar depression